Clinical Infectious Diseases

MAJOR ARTICLE

Early antiretroviral therapy not associated with higher cryptococcal meningitis mortality in people with HIV in high-income countries: an international collaborative cohort study

Suzanne M. Ingle[1]*, Jose M. Miro[2,3]*, Margaret T. May[1], Lauren E. Cain[4,5], Christine Schwimmer[6], Robert Zangerle[7], Helen Sambatakou[8], Charles Cazanave[9], Peter Reiss[10], Vanessa Brandes[11], Heiner C. Bucher[12], Caroline Sabin[13], Francesc Vidal[14], Niels Obel[15], Amanda Mocroft PhD[16], Linda Wittkop[17], Antonella D'arminio Monforte[18], Carlo Torti[19], Cristina Mussini[20], Hansjakob Furrer[21], Deborah Konopnicki[22], Ramon Tiera[23], Michael S. Saag[24], Heidi M. Crane[25], Richard D. Moore[26], Jeffrey M. Jacobson[27], W. Chris Mathews[28], Elvin Geng[29], Joseph J. Eron[30], Keri N. Althoff[31], Abigail Kroch[32], Raynell Lang[31], M. John Gill[33] and Jonathan A.C. Sterne[1] on behalf of ART-CC, COHERE in EuroCoord, CNICS and NA-ACCORD.

[1:] Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; [2:] Infectious Diseases Service Hospital Clinic – IDIBAPS. University of Barcelona. Barcelona, Spain; [3:] CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain; [4:] Department of Epidemiology, Harvard T.H. Chan School of Public Health; [5:] Global Epidemiology, AbbVie ; [6:] Univ. Bordeaux, INSERM, Institut Bergonié, CHU de Bordeaux, CIC-EC 1401, F-33000 Bordeaux, France ; [7:] Medical University Innsbruck, Innsbruck, Austria; [8:] HIV unit, 2nd Dept of Internal Medicine, Medical School, National & Kapodistrian University of Athens, Hippokration General Hospital. Athens, Greece; [9:] CHU de Bordeaux, Infectious and Tropical Diseases Department, F-33000 Bordeaux, France; [10:] Stichting HIV Monitoring, Amsterdam, the Netherlands; [11:] Department I of Internal Medicine, Division of Infectious Diseases, University of

*Contributed equally.

Correspondence: Jose M. Miro. Infectious Diseases Service. Hospital Clinic. Villarroel, 170. 08036 Barcelona, Spain. E-mail address: jmmiro@ub.edu

© The Author(s) 2023. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

DOI: 10.1093/cid/ciad122

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

source: https://doi.org/10.48350/179749 | downloaded: 12.10.2024

Cologne, Cologne, Germany; [12:] Basel Institute for Clinical Epidemiology & Biostatistics, Division of Infectious Diseases & Hospital Hygiene, University Hospital Basel, Basel, Switzerland; [13:] Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College London, UK; [14:] Hospital Universitari de Tarragona Joan XXIII, IISPV, Universitat Rovira i Virgili, Tarragona, Spain. CIBER Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain; [15:] Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [16:] Centre of Excellence for Health, Immunity and Infections (CHIP) and PERSIMUNE, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [17:] ISPED, INSERM, Bordeaux Population Health Research Center, University of Bordeaux, Bordeaux, France; [18:] Clinic of Infectious and Tropical Diseases, University of Milan, Department of Health Sciences, S Paolo Hosp, Milan, Italy; [19:] Department of Surgical and Medical Sciences, Chair of Infectious and Tropical Diseases, University "Magna Graecia", Catanzaro, Italy; [20:] University of Modena and Reggio Emilia, Modena, Italy; [21:] Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [22:] Infectious Diseases deprtament, Saint-Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium ; [23:] Service of Internal Medicine, Hospital Universitario de Sierrallana, Torrelavega, Spain; [24:] Center for AIDS Research, University of Alabama at Birmingham, Alabama, US; [25:] Division of Infectious Diseases, Department of Medicine University of Washington, Seattle, WA, US; [26:] School of Medicine, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [27:] Case Western Reserve University, Cleveland, Ohio, US; [28:] University of California San Diego, Department of Medicine, US; [29:] Division of Infectious Diseases, Department of Medicine and the Center for Dissemination and Implementation, Institute for Public Health, Washington University in St. Louis; [30:] UNC School of Medicine, Chapel Hill, NC, US; [31:] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US; [32:] University of Toronto, Canada; [33:] Department of Medicine, University of Calgary, S Alberta HIV Clinic, Canada

Background: Randomized trials (RCTs) from low- and middle-income settings suggested early initiation of antiretroviral therapy (ART) leads to higher mortality among people with HIV (PWH) who present with cryptococcal meningitis (CM). There is limited information about impact of ART timing on mortality in similar people in high-income settings.

Methods: Data on ART-naïve PWH diagnosed with CM from 1994-2012 from Europe/North America were pooled from the COHERE, NA-ACCORD and CNICS HIV cohort collaborations. Follow-up was considered from the date of CM diagnosis to earliest of the following: death, last follow-up or 6 months. We used marginal structural models to mimic an RCT comparing effects of early (within 14 days of CM) with late (14-56 days after CM) ART on all-cause mortality, adjusting for potential confounders.

Results: Of 190 participants identified, 33 (17%) died within 6 months. At CM diagnosis, median age was 38 years (interquartile range 33-44); CD4 count was 19 cells/mm^3 (10-56); and HIV viral load was 5.3 $\log_{10}$ copies/mL (4.9-5.6). Most participants (157, 83%) were males and

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

145 (76%) started ART. Mimicking an RCT, with 190 people in each group, there were 13 deaths among participants following early ART regimen and 20 deaths among those following late ART regimen. Crude and adjusted hazard ratios comparing late with early ART were 1.28 (95% CI: 0.64, 2.56) and 1.40 (0.66, 2.95).

Conclusions: We found little evidence that early ART was associated with higher mortality among PWH presenting with CM in high income settings, although confidence intervals were wide.

Keywords: HIV, cryptococcal meningitis, ART, causal inference

INTRODUCTION

Cryptococcal meningitis (CM) is a common opportunistic infection (OI) in people living with HIV (PWH) and has high mortality. In 2014, over 200,000 incident cases of CM were globally among PWH, with over 180,000 deaths, most in sub-Saharan Africa[1].

For antiretroviral therapy (ART) naïve patients presenting with CM, ART should be administered once antifungal treatment has started. However, there is conflicting evidence from randomised clinical trials (RCTs) on the optimal time to initiate ART. Two African RCTs concluded that early ART (within 15 days of starting OI treatment) was associated with increased mortality compared with late ART[2, 3]. A Chinese RCT[4] also showed increased mortality with early ART, although that study used different definitions (early ART: within 2-5 weeks after starting OI treatment, late ART: 5 weeks after OI treatment). Conversely, ACTG A5164, conducted in the USA and South Africa[5], found that early ART (within 14 days), resulted in reduced progression to AIDS and fewer deaths than late ART (after completion of OI treatment). A post-hoc analysis, restricted to participants with CM, suggested a beneficial effect of early ART, although sample size was small. When considering other aetiologies of meningitis, an RCT in Vietnam[6] found that early ART did not decrease mortality in PWH with *Mycobacterium tuberculosis* meningitis. A 2018 Cochrane review, found insufficient evidence in support of either early or late ART in PWH with CM[7]. Current WHO advice states “immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have CM because of the risk of increased mortality”[8].

As data regarding this issue in high-income settings is lacking, observational data were analysed using marginal structural models to mimic a clinical trial of when to start ART in PWH with CM diagnosed in high-income settings.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

METHODS

Data on ART-naïve (no prior ART use) PWH diagnosed with CM between 1994 and 2012 were combined from the COHERE[9], NA-ACCORD[10] and CNICS[11] collaborations of clinical HIV cohorts from Europe and North America. To avoid duplication between NA-ACCORD and CNICS, the record from NA-ACCORD was used. Participants were eligible if, at CM diagnosis: they were ≥16 years old, and CD4+ count and viral load (VL) measures were available. Additionally, follow-up data were required after CM diagnosis (records present regarding lab tests/visits/mortality, bloods were taken every 3 months on average across these settings). CM diagnosis was based on the 1993 Centers for Disease Control clinical case definition[12]. The outcome was all-cause mortality.

Variables

Baseline was defined as the date of CM diagnosis. Baseline CD4+ count and VL were the values closest to CM diagnosis date within a window of three months prior to and one week post diagnosis. Baseline CD4+ counts were low, so were categorised as 0-9, 10-19, 20-49, 50-99 and 100+ cells/mm^3. Time-updated CD4+ counts were higher, and categorised as: 0-49, 50-99, 100-199, 200-349, 350-499 and ≥500 cells/mm^3. Baseline and time-updated $\log_{10}$VL were categorised as 0-3.99, 4-4.99 and ≥5; and 0-1.69, 1.70-3.99 and ≥4 copies/mL respectively. Other variables included were: sex; age; probable mode of HIV acquisition (injecting drug use (IDU), sex between men, sex between men and women, unknown); diagnosis of AIDS before baseline (excluding CM), calendar year of CM diagnosis (1994-99, 2000-01, 2002-04, 2005 and later) and location (Europe, North America). Follow-up was from CM diagnosis date to the earliest of death, last follow-up or 6 months post-diagnosis. Follow-up was censored at 6 months as an effect of ART timing beyond this was deemed unlikely.

Mimicking an RCT

We used marginal structural models to mimic an RCT of the effect of ART timing on all-cause mortality. We compared regimen A) start ART within 14 days of CM diagnosis (early ART), with B) defer ART until 15-56 days after CM diagnosis (late ART). We used the three-stage (clone, censor, weight) approach described by Cain[13] and Hernán[14]. First, we replicated (cloned) the data for each participant; one clone was assigned to each regimen. Second, data for each clone were censored if the person deviated from the regimen assigned to that clone. For example, a person starting ART on day 10 adhered to regimen A throughout follow-up and so data for the clone assigned to this regimen remained uncensored. Data for the clone assigned to regimen B was censored on day 10, when the person deviated from regimen B. Third, to avoid selection bias caused by the censoring process, the analysis used inverse probability weights, based on the cumulative probability of remaining uncensored. Because censoring was based on being treated with ART, the probability of being censored was estimated from a model for the probability of starting ART over time since CM diagnosis.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

To derive weights, CD4+ and VL values were carried forward for a maximum of six months in the absence of more recent measures. Inverse-probability-of-treatment weights (IPTW) were derived using a pooled logistic regression model for starting ART on the uncloned data. We used multivariable fractional polynomials (MFP) to allow flexibility in the functional form of time and other continuous covariates. We included all variables listed above.

Using the model described above, we predicted the probability of starting ART for each day each person was in the study, assuming that ART was continued once started. Treatment probabilities were multiplied to derive the probability of each person's observed treatment history on each day. To stabilise the IPTW, we fitted a further pooled logistic regression model, omitting the time-updated variables. The probabilities of observed treatment history from this model were multiplied by the unstabilised weights.

Fitting the marginal structural model

A pooled logistic regression model, weighted by the stabilised IPTW, was used to estimate the mortality hazard ratio (HR) comparing late versus early (reference group) ART. The model was adjusted for time (day and day squared), and baseline variables. Robust standard errors allowed for clustering by participant.

Sensitivity analyses

Missing baseline values of CD4+ count or VL were imputed by modelling their trajectories from baseline to 6 months post-diagnosis, for those with and without baseline measures. Imputation used the twofold fully conditional specification algorithm via the twofold command in Stata[15]; this imputes missing values at particular time points (baseline, 2, 4 and 6 months, with a window period of +/- 4 weeks for each measurement) given data available at that time point and at adjacent time points. CD4 was square-root transformed and VL was log-transformed for the imputations. We fitted the model to generate IPTW and the final marginal structural model for mortality on each of 25 imputed datasets; Rubin's rules[16] were used to combine results over datasets.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

Data were available from 30 cohorts across Europe and North America (Supplementary Table 1) with a majority of participants from the USA and Spain. Figure 1 shows a flow chart of PWH included in the analysis, leaving 190 participants with full covariate data. Comparing characteristics of the 190 included PWH with those excluded for reasons other than being ART-

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

experienced showed that: participants in European cohorts, females, those who acquired HIV through sex between men and women and those diagnosed with CM in earlier calendar periods were more likely excluded (Supplementary Table 2).

Table 1 shows characteristics of those included and compares them by ART and mortality status by six months post-diagnosis. Most participants were male (83%) and acquired HIV through a sexual route. At CM diagnosis, median age was 38 years (interquartile range (IQR) 33-44), CD4+ count was 19 cells/mm^3 (IQR:10-56) and VL was 5.3 $\log_{10}$ copies/mL (IQR:4.9-5.6).

Of 190 PWH, 145 (76%) started ART within six months of CM diagnosis; most initiated a protease inhibitor (PI)-based regimen and median time from CM diagnosis to ART start was 23 days (IQR:6-42). Thirty-three people (17%) died within six months of CM diagnosis, 16 of 145 (11%) on ART and 17 of 45 (38%) not on ART; 45% of deaths were from CM or other AIDS-defining events and 42% from unspecified causes. Four people died from non-AIDS-defining causes. Characteristics of people who died within six months were broadly similar to those who did not, although the former group was older and more likely from European cohort studies.

Table 2 shows characteristics for each arm of the mimicked trial, in which data from all 190 participants were cloned and included in each trial arm, with follow-up censored when they deviated from that arm. Eight deaths were excluded from the mimicked trial because follow-up was censored: four in people who started ART after day 56 and 4 in people who died after day 56 without starting ART. Eight deaths that occurred before starting ART and within two weeks of CM were included in both arms, because they occurred in individuals whose follow-up was consistent with both arms. We refer to these as “duplicated deaths”. After censoring, there were 13 deaths under early ART (5 among people who started ART within 2 weeks and died by 6 months, and 8 duplicated deaths) and 20 deaths under late ART (5 among people not on ART who died by day 56, 7 among people who started ART within days 15-56 but died by 6 months, and 8 duplicated deaths). In the early ART arm, after censoring, 56 participants started ART within 2 weeks of CM diagnosis, among whom most started ART immediately (median 0 days, IQR:0-7, between diagnosis and ART start). In the late ART arm (after censoring), 68 participants started ART between 2 and 8 weeks after diagnosis. Among these, median time to starting ART was 31 days (IQR:23-42). Participants in the early ART arm were more likely to initiate a PI-based therapy and to die of an AIDS event than those in the late ART arm. More deaths were from unknown causes in the late ART arm.

Supplementary Table 3 compares longitudinal CD4+ count and VL values among participants after imputation of missing values with those with complete data. Whilst baseline values were similar, follow-up VL values were generally higher in the imputed dataset than in the complete-case dataset, suggesting those with complete data may represent participants with less advanced HIV.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

Figure 2 shows Kaplan-Meier survival estimates from mimicking an RCT by cloning and censoring the data. Survival patterns were similar for the two arms, with overlapping confidence intervals (CIs), although by the end of follow-up mortality was slightly worse among the late ART arm. At one month, estimated survival was 94% (95% CI 88-97) in the early ART arm and 92% (86-95) in the late ART arm, with corresponding figures at six months 87% (77-93) and 82% (73-88), respectively.

In constructing marginal structural models, IPTW were derived by fitting an MFP model to predict who starts ART at each time point. Model estimates are in Supplementary Table 4. Supplementary Figure 1 shows a box plot of the stabilised weights.

Crude and adjusted mortality HRs comparing late with early ART were 1.28 (95% CI: 0.64, 2.56) and 1.40 (0.66, 2.95). Analyses using imputed data gave an attenuated adjusted mortality HR of 1.17 (0.72, 1.91).

Comparisons with published rcts

Table 3 compares the present study (further details in Supplementary Table 5) with three RCTs on ART timing among PWH with OIs. The Zimbabwean RCT[3] found early ART was detrimental (HR 0.35 (95% CI 0.14-0.91)): mortality risks in participants treated early (<72 hours) and late (>10 weeks) were 82% and 46%, respectively. A potential limitation was that participants were treated with fluconazole, a suboptimal therapy for induction. Furthermore, definitions of early and late ART were different. The COAT trial[2], included PWH with CM in Uganda and South Africa treated with amphotericin B plus fluconazole for induction. It found similar results to the Zimbabwe trial (HR 0.26 (0.09-0.71)). Mortality in people initiating ART within 1-2 weeks and deferring ART for 5 weeks after CM diagnosis were 47% and 33% respectively. Most PWH who died did so within the first 2-5 weeks.

The ACTG A5164 trial[5] combined data from the USA and South Africa. It found that late ART after OI treatment is complete resulted in higher rates of progression to AIDS and death than early ART (within 15 days of starting OI treatment) (HR 1.96 (1.06-3.06)). Although most participants had PCP, post-hoc analysis suggested the beneficial effect of early ART persisted for CM. No participants in the early ART arm died, whereas 17% in the late ART arm died.

DISCUSSION

We found little evidence that early ART after CM was associated with higher mortality than late ART in ART-naïve PWH living in high-income settings. Mortality rates in this study were markedly lower than those in African RCTs. People in this study and the three RCTs were young - median age ranged from 35 to 43 years. Women represented 48% of participants in African RCTs but only 16% in our study and the ACTG trial. There is evidence that women with HIV experience higher mortality in CM [17] which may partly explain mortality differences across

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

settings. All African patients reported HIV acquisition through heterosexual routes, whereas in our study 34% of HIV acquisition was through sex with men.

Access to healthcare and severity of CM may be relevant to the effect of early ART. In Africa, contact with healthcare tends to occur later, when CM is more severe with higher deterioration in consciousness and higher fungal load in the central nervous system. These factors, together with the lack of cells in cerebrospinal fluid (CSF), are associated with worse prognosis[6, 18]. Our study did not benefit from clinical or laboratory data, but we know levels of immunosuppression and plasma HIV-VL at diagnosis were similar in all four studies. The number of CD4+ lymphocytes is inversely proportional to CSF fungal load[19], especially when CD4>100 cells/mm^3. However, median CD4+ lymphocytes in these studies ranged from 19–51 cells/mm^3. Plasma HIV-VL was around 100,000 copies/mL, implying participants had advanced HIV disease.

Type of antifungal treatment administered is a likely explanation for mortality differences between studies. Since the 1990s, amphotericin B has been the treatment of choice for AIDS-associated CM in the USA, Europe and other developed settings and flucytosine has been added during the first two weeks whenever there were no contraindications especially since 2000[20]. This combination is fungicidal and superior in terms of mortality to: amphotericin B monotherapy, combined amphotericin B and fluconazole, combined fluconazole and flucytosine, and fluconazole monotherapy[21, 22]. RCTs in high-income settings with amphotericin B and flucytosine induction at 10 weeks had 9% mortality[23], similar to our study. In Africa and other low-income settings with no access to these two essential drugs[24], the fungistatic fluconazole was used at induction. Two RCTs in low-income settings[21, 22] that compared induction with amphotericin B and flucytosine (control arm) with*:* fluconazole and flucytosine, amphotericin B and fluconazole and amphotericin B monotherapy, reported 10-week mortality rates of 24%, 30%, 35%, 33% and 44%, respectively. The Zimbabwean RCT[3] used fluconazole as monotherapy, which may explain the high mortality. The COAT trial[2] used amphotericin B and fluconazole at induction, and had similar mortality to the two African RCTs[21, 22].

Other potential explanations for the mortality difference include non-systematic use of lumbar puncture to reduce intracranial hypertension. This intervention, which reduces mortality[25], was only practised in the COAT trial[2]. Second, IRIS is associated with early ART in high-risk people (low CD4+ counts, high plasma HIV-VLs, high CSF fungal inoculum). Up to 50% of people with CM who start ART early (<2 weeks) develop paradoxical IRIS that can worsen prognosis[26]. The most important predictor of not developing CM-IRIS is a negative CSF culture for *Cryptococcus neoformans* when starting ART. A South African study showed the rate of CM-IRIS was reduced by 60% in people with negative CSF culture at ART start[27]. Therefore, CM-IRIS risk is lower in people receiving induction treatment with two antifungals. Several studies have shown the probability of inducing negative CSF culture in the first two weeks is higher with combination amphotericin B and flucytosine[21, 22]. In African studies[5, 6] the most important cause of mortality was CM itself, whereas it was rare in high-income

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

settings[7], supporting use of this combination of antifungals. Third, type of ART differed across settings. In Africa, people only received ART based on efavirenz or nevirapine, whereas our study and the ACTG predominantly used PIs. Although these ART regimens do not influence risk of IRIS[28], HIV PIs can inhibit *in vitro* the production of virulence factors of *C. neoformans* and therefore might improve CM prognosis[29].

Two other relevant factors are subtypes of *C. neoformans* and antifungal resistance. A recent study sequencing isolates of *C. neoformans* from PWH in Asia and Africa showed an expansion of three subclades of the *C. neoformans* VNIa lineage: VNIa-4, VNIa-5, and VNIa-93[30]. VNIa-93 was most common in Uganda and Malawi and was associated with better prognosis than VNIa-4 and VNIa-5 subclades, which predominated in Southeast Asia. It is unknown which subclades predominate in high-income settings, but the fact that in Africa a subclade with better prognosis predominates does not explain the worse prognosis observed in CM. There is scant data on antifungal resistance in Africa. A Ugandan study[31] showed no resistance to amphotericin B but a loss of sensitivity to fluconazole over time, with 31% of isolates in later years having a fluconazole MIC of ≥ 16/ml.

Strengths and Limitations

Our sample, whilst being a selected sample of the total population, is representative of PWH in care in high-income settings, whereas current guidelines are based on low-income settings. The main reason for exclusion from analyses was that follow up data was not available for 256 of 630 potentially eligible PWH. We used statistical methods that mimic a trial using observational data, and should avoid biases such as immortal time or lead-time bias. A similar approach was used in observational data from Latin America[32] which similarly found no evidence of a detrimental effect of early ART (< 2 weeks).

Although we adjusted for potential confounding factors, unmeasured confounding is always possible in observational studies. We had no information on clinical characteristics (severity of disease, Glasgow coma score), antifungal treatment, intracranial pressure monitoring, use of steroids (the negative impact of steroids only emerged after the trial from Vietnam[6]), reasons for timing of ART initiation other than those accounted for in our analyses, or monitoring of CM progression. The age of our data may be an issue, though antifungal therapy has not changed in three decades. Despite collating data from large collaborations, the sample size was small.

Implications and conclusions

We did not find evidence that early ART within two weeks of CM diagnosis led to higher mortality among PWH presenting with CM in high income settings.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

NOTES

Contributors:

JMM, HF, MM and JACS conceived and designed the study. SMI combined, checked, cleaned, and verified the datasets. All authors contributed to derivation, cleaning, and provision of cohort data. SMI did all statistical analyses with guidance from LC, MM and JACS. SMI and JMM wrote the original draft of the manuscript. All authors interpretated the data and critically revised the manuscript for important intellectual content. SMI and MM accessed and verified the combined dataset. The individual cohort representatives could access the data from their own cohort.

Acknowledgements:

Dr. William Powderly, M.D.from Division of Infectious Diseases, Washington University in St. Louis, Missouri for managing and provindig the data of patients with cryptococal meningitis from the ACTG A5164 clinical trial. To Dr. David Boulware from University of Minnesota, Minneapolis, Minnesota for providing the data on patients with cryptococal meningitis from the COAT clinical trial. JMM received a personal 80:20 research grant from Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, during 2017–23. FV is supported by grants from the Programa de Intensificación de Investigadores (INT20/00031)-ISCIII and form the Premi a la Trajectòria Investigadora dels Hospitals de l'ICS 2018.

Art-cc

We would like to thank our funders (US National Institute on Alcohol Abuse and Alcoholism and UK Medical Research Council) and all patients and the clinical teams associated with the participating cohort studies. The Antiretroviral Therapy Cohort Collaboration is funded by the US National Institute on Alcohol Abuse and Alcoholism (U01-AA026209). JACS is funded by National Institute for Health Research Senior Investigator award (NF-SI-0611-10168).

Cnics

CNICS is an NIH funded program (R24 AI067039) made possible by the National Institute of Allergy and Infectious Diseases (NIAID). The CFAR sites involved in CNICS include Univ of Alabama at Birmingham (P30 AI027767), Univ of Washington (P30 AI027757), Univ of California San Diego (P30 AI036214), Univ of California San Francisco (P30 AI027763), Case Western Reserve Univ (P30 AI036219), Johns Hopkins Univ (P30 AI094189, U01 DA036935), Fenway Health/Harvard (P30 AI060354), Univ of North Carolina Chapel Hill (P30 AI50410), Vanderbilt Univ (P30 AI110527)*****, and Univ of Miami (P30 AI073961)*****.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

Na-accord

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This work was supported by National Institutes of Health grants U01AI069918, F31AI124794, F31DA037788, G12MD007583, K01AI093197, K01AI131895, K23EY013707, K24AI065298, K24AI118591, K24DA000432, KL2TR000421, N01CP01004, N02CP055504, N02CP91027, P30AI027757, P30AI027763, P30AI027767, P30AI036219, P30AI050409, P30AI050410, P30AI094189, P30AI110527, P30MH62246, R01AA016893, R01DA011602, R01DA012568, R01 AG053100, R24AI067039, U01AA013566, U01AA020790, U01AI038855, U01AI038858, U01AI068634, U01AI068636, U01AI069432, U01AI069434, U01DA03629, U01DA036935, U10EY008057, U10EY008052, U10EY008067, U01HL146192, U01HL146193, U01HL146194, U01HL146201, U01HL146202, U01HL146203, U01HL146204, U01HL146205, U01HL146208, U01HL146240, U01HL146241, U01HL146242, U01HL146245, U01HL146333, U24AA020794,U54MD007587, UL1RR024131, UL1TR000004, UL1TR000083, Z01CP010214 and Z01CP010176; contracts CDC-200-2006-18797 and CDC-200-2015-63931 from the Centers for Disease Control and Prevention, USA; contract 90047713 from the Agency for Healthcare Research and Quality, USA; contract 90051652 from the Health Resources and Services Administration, USA; grants CBR-86906, CBR-94036, HCP-97105 and TGF-96118 from the Canadian Institutes of Health Research, Canada; Ontario Ministry of Health and Long Term Care; and the Government of Alberta, Canada. Additional support was provided by the National Institute Of Allergy And Infectious Diseases (NIAID), National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD), National Human Genome Research Institute (NHGRI), National Institute for Mental Health (NIMH) and National Institute on Drug Abuse (NIDA), National Institute On Aging (NIA), National Institute Of Dental & Craniofacial Research (NIDCR), National Institute Of Neurological Disorders And Stroke (NINDS), National Institute Of Nursing Research (NINR), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Deafness and Other Communication Disorders (NIDCD), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Cohere

The COHERE study group has received unrestricted funding from: the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; the HIV Monitoring Foundation, The Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. A list of the funders of the participating cohorts can be found at www.COHERE.org.

Data sharing: Due to the data sharing agreements between individual cohorts and the collaborations (ART-CC, COHERE, NA-ACCORD and CNICS), the data collected for this

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

study cannot be shared. Data are owned by the individual cohorts, and those wishing to access these data should contact the individual cohorts.

Funding: Funding: UK-MRC (reported by SMI and MTM), NIH [reported by KA, JJE, RDM, JACS, MJG, HC, and LEC]. SMI and MTM reports support from NIAAA. RTC reports support from University of Bristol (funding for data extraction). AM reports the COHERE study group has received unrestricted funding from: the Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; the HIV Monitoring Foundation, The Netherlands; and the Augustinus Foundation, Denmark. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. A list of the funders of the participating cohorts can be found at www.COHERE.org (UCL /CHIP received institutional funding from COHERE) MSS reports support from ART-CC (international cohort).

Declaration of Interests: JMM has received consulting honoraria and/or research grants from AbbVie, Angelini, Contrafect, Cubist, Genentech, Gilead Sciences, Jansen, Medtronic, MSD, Novartis, Pfizer, and ViiV Healthcare, outside the submitted; including consulting fees from Lysovant. LEC has stock or stock option and is an employee of AbbVie. FV received research or teaching grants from Gilead Sciences, ViiV Healthcare and MSD not related with the submitted work. PR through his institution has received independent scientific grant support from Gilead Sciences, Janssen Pharmaceuticals Inc, Merck & Co and ViiV Healthcare, and has served on scientific advisory boards for Gilead Sciences, ViiV Healthcare, and Merck & Co honoraria for which were all paid to his institution, all outside the submitted work. The institution of HF received educational grants from AbbVie, ViiV, Gilead, MSD, Sandoz, Pfizer outside the submitted work. AM declares travel support, lecture fees, honorarium and consultancy fees from ViiV, Gielad, Eiland and Bonnin, all outside the submitted work. CM reports research grant from Gilead, payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from ViiV and Gilead, and participation on a Data Safety Monitoring Board or Advisory Board for Corimuno, Gilead, ViiV, Janssen, and MSD. ADM reports consulting fees from ViiV, Gilead, Jannsen (paid to author), payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from Gilead (paid to author), and ViiV (paid to author), participation on a Data Safety Monitoring Board or Advisory Board for Jannsen, Gilead, and ViiV (paid to author). KNA reports grants or contracts from NIH (paid to institution), royalties or lincenses from Coursera, consulting fees from NIH (consultant to the All of US Study), and payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events for DC HIV Cohot (author served on the external advisory board of the DC HIV Cohort). JJE reports grants or contracts from ViiV Healthcare, Gilead Sciences, and Jannsen, consulting fees from Merck, ViiV Healthcare, Gilead Science, and Jannsen and reports a Leadership or fiduciary role in other board, society, committee or advocacy group for IAS-USA Antiretroviral therapy guidelines committee. LW reports grants or contracts from ANRS MIE. NO reports grants or contracts from Simonsens Fond (paid to

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

institution). CS reports payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from Gilead Sciences and ViiV Healthcare (payments to author for preparation of educational materials), participation on a Data Safety Monitoring Board or Advisory Board for Glead Sciences and ViiV Healthcare (paid to author) and is the Vice-chair for the British HIV Association. HS reports consulting fees from ViiV and MSD, and payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from MSD, ViiV, and Gilead. RTC reports research grant from Gilead Science, payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from Gilead Science (paid for lectures), Jannsen (paid for lectures), and ViiV Healthcare (paid for lectures), support for travel from Gilead Science and Jannsen, and participation on a Advisory Board for Gilead Science. MJG reports consulting fees from Merck (Occasional Honorarium to me for ad hoc membership of HIV advisory Board), Gilead (Occasional Honorarium to me for ad hoc membership of HIV advisory Board), and ViiV (Occasional Honorarium to me for ad hoc membership of HIV advisory Board). HC reports grants or contracts from NIH, AHRQ, and ViiV (paid to institution), consulting fees from ViiV (pending), and is an advisory board for the Office of AIDS Research Scientific. HCB has received in the 36 months prior to the submission of this manuscript grants, support for travelling, consultancy fees and honorarium from Gilead, BMS, Viiv Healthcare, Roche and Pfizer that were not related to this project. He served as the president of the association contre le HIV et autres infections transmissibles until June 2022.

In this function he had received support for the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, BMS, and MSD. MSS reports research grant from Gilead Sciences and ViiV Healthcare (paid to institution) payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from IAS-USA (not for profit organization), DSMB for I-Spy COVID trial, and is a board chair for IAS-USA (not for profit organization) VB reports support for attending meetings and/or travel from Online

Registration Fee CROI 2021 (Gilead), and Attendance and Travel costs 18, Munich AIDS and COVID days 2022 (Jannsen), and has stock or stock options for DWS Biotech LC Fond (private self-investment. Not paid to author or institution from any third party received).

References:

1. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis **2017**; 17(8): 873-81.
2. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med **2014**; 370(26): 2487-98.
3. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis **2010**; 50(11): 1532-8.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

4. Zhao T, Xu XL, Lu YQ, et al. The Effect of Early vs. Deferred Antiretroviral Therapy Initiation in HIV-Infected Patients With Cryptococcal Meningitis: A Multicenter Prospective Randomized Controlled Analysis in China. Front Med (Lausanne) **2021**; 8: 779181.
5. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One **2009**; 4(5): e5575.
6. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. Clin Infect Dis **2011**; 52(11): 1374-83.
7. Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev **2018**; 7: CD009012.
8. WHO. Guidelines for The Diagnosis, Prevention and Management of Cryptococcal Disease in HIV-Infected Adults, Adolescents and Children: Supplement to the 2016 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Geneva, **2018**.
9. Chene G, Phillips A, Costagliola D, et al. Cohort Profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. Int J Epidemiol **2017**; 46(3): 797-n.
10. Gange SJ, Kitahata MM, Saag MS, et al. Cohort profile: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Int J Epidemiol **2007**; 36(2): 294-301.
11. Kitahata MM, Rodriguez B, Haubrich R, et al. Cohort profile: the Centers for AIDS Research Network of Integrated Clinical Systems. Int J Epidemiol **2008**; 37(5): 948-55.
12. CDC. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. CDC Morbidity and Mortality Weekly Report **1992**; 41(RR-17).
13. Cain LE, Robins JM, Lanoy E, Logan R, Costagliola D, Hernan MA. When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data. Int J Biostat **2010**; 6(2): Article 18.
14. Hernan MA. How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ **2018**; 360: k182.
15. Welch CA, Petersen I, Bartlett JW, et al. Evaluation of two-fold fully conditional specification multiple imputation for longitudinal electronic health record data. Stat Med **2014**; 33(21): 3725-37.
16. Rubin D. Multiple imputation for nonresponse in surveys. New York: Wiley, **1987**.
17. Stadelman AM, Ssebambulidde K, Tugume L, et al. Impact of biological sex on cryptococcal meningitis mortality in Uganda and South Africa. Med Mycol **2021**; 59(7): 712-9.
18. Hakyemez IN, Erdem H, Beraud G, et al. Prediction of unfavorable outcomes in cryptococcal meningitis: results of the multicenter Infectious Diseases International Research Initiative (ID-IRI) cryptococcal meningitis study. Eur J Clin Microbiol Infect Dis **2018**; 37(7): 1231-40.
19. Tugume L, Rhein J, Hullsiek KH, et al. HIV-Associated Cryptococcal Meningitis Occurring at Relatively Higher CD4 Counts. J Infect Dis **2019**; 219(6): 877-83.
20. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis **2000**; 30(4): 710-8.
21. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med **2018**; 378(11): 1004-17.

ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

22. Day JN, Chau TTH, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med **2013**; 368(14): 1291-302.
23. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med **1997**; 337(1): 15-21.
24. Loyse A, Burry J, Cohn J, et al. Leave no one behind: response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle-income countries. Lancet Infect Dis **2019**; 19(4): e143-e7.
25. Rolfes MA, Hullsiek KH, Rhein J, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. Clin Infect Dis **2014**; 59(11): 1607-14.
26. Bisson GP, Molefi M, Bellamy S, et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. Clin Infect Dis **2013**; 56(8): 1165-73.
27. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. AIDS **2013**; 27(13): 2089-99.
28. Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. PLoS One **2010**; 5(7): e11416.
29. Sidrim JJ, Perdigao-Neto LV, Cordeiro RA, et al. Viral protease inhibitors affect the production of virulence factors in Cryptococcus neoformans. Can J Microbiol **2012**; 58(7): 932-6.
30. Ashton PM, Thanh LT, Trieu PH, et al. Three phylogenetic groups have driven the recent population expansion of Cryptococcus neoformans. Nat Commun **2019**; 10(1): 2035.
31. Smith KD, Achan B, Hullsiek KH, et al. Increased Antifungal Drug Resistance in Clinical Isolates of Cryptococcus neoformans in Uganda. Antimicrob Agents Chemother **2015**; 59(12): 7197-204.
32. Crabtree Ramirez B, Caro Vega Y, Shepherd BE, et al. Outcomes of HIV-positive patients with cryptococcal meningitis in the Americas. Int J Infect Dis **2017**; 63: 57-63

.

ACCECPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

Table 1: Demographics, clinical characteristics and 6-month outcomes (N (%)) among 190 eligible PWH with cryptococcal meningitis (CM)

		Overall (N=190)	ART by 6 months (N=145)	No ART by 6 months (N=45)	p-value	Alive at 6 months (N=157)	Dead at 6 months (N=33)	p-value
Location	Europe	114 (60.0)	94 (64.8)	20 (44.4)	0.015	88 (56.1)	26 (78.8)	0.015
	North America	76 (40.0)	51 (35.2)	25 (55.6)		69 (43.9)	7 (21.2)	
Sex	Male	157 (82.6)	122 (84.1)	35 (77.8)	0.33	129 (82.2)	28 (84.9)	0.71
	Female	33 (17.4)	23 (15.9)	10 (22.2)		28 (17.8)	5 (15.2)	
Age, years	Median (IQR)	38 (33-44)	38 (33-43)	40 (34-44)	0.70	38 (34-43)	43 (32-48)	0.021
Race	Black	55 (28.9)	37 (25.5)	18 (40.0)	0.17	43 (27.4)	12 (36.4)	0.45
	White	55 (28.9)	64 (44.1)	16 (35.6)		48 (30.6)	7 (21.2)	
	Other/unknown	80 (42.1)	44 (30.3)	11 (24.4)		66 (42.0)	14 (42.4)	
Mode of HIV acquisition	Sex between men	65 (34.2)	55 (37.9)	10 (22.2)	0.26	54 (34.4)	11 (33.3)	0.81
	Injecting Drug Use	28 (14.7)	20 (13.8)	8 (17.8)		24 (15.3)	4 (12.1)	
	Sex between men and women	72 (37.9)	51 (35.2)	21 (46.7)		60 (38.2)	12 (36.4)	
	Other/unknown	25 (13.2)	19 (13.1)	6 (13.3)		19 (12.1)	6 (18.2)	
Year of CM diagnosis	1994-1999	25 (13.2)	19 (13.1)	6 (13.3)	0.97	19 (12.1)	6 (18.2)	0.59
	2000-2001	42 (22.1)	32 (22.1)	10 (22.2)		35 (22.3)	7 (21.2)	
	2002-2004	67 (35.3)	50 (34.5)	17 (37.8)		54 (34.4)	13 (39.4)	
	2005+	56 (29.5)	44 (30.3)	12 (26.7)		49 (31.2)	7 (21.2)	
Previous AIDS diagnosis		78 (41.1)	61 (42.1)	17 (37.8)	0.61	63 (40.1)	15 (45.5)	0.57
CD4+ T-cell count at CM diagnosis, cells/mm^3	Median (IQR)	19 (10-56)	20 (10-57)	17 (9-38)	0.35*	20 (10-61)	15 (9-32)	0.22*
VL at CM diagnosis, $\log_{10}$ copies/mL	Median (IQR)	5.3 (4.9-5.6)	5.3 (4.9-5.6)	5.4 (5-5.6)	0.44*	5.3 (4.9-5.6)	5.4 (4.8-5.8)	0.32*
ART within 6 months of CM diagnosis	No	45 (24%)	··	··	··	24 (53%)	21 (47%)	<0.01
	Yes	145 (76%)	··	··		133 (92%)	12 (8%)	
Median (IQR) days from CM diagnosis to ART		23 (6-42)				23 (5-42)	23 (12-45)	0.99*
Type of ART received (n=145)	PI based	82 (56.6)	82 (56.6)	··		74 (57.4)	8 (50.0)	0.84
	NNRTI based	53 (36.6)	53 (36.6)	··		46 (35.7)	7 (43.8)	

ACCEPTED MANUSCRIPT

DOI: 10.1093/cid/ciad122

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

	NRTIs only	3 (2.1)	3 (2.1)	··		3 (2.3)	0 (0)	
	Other	7 (4.8)	7 (4.8)	··		6 (4.7)	1 (6.3)	
Causes of death (n=33 within 6 months)	AIDS defining events	15 (45.5)	4 (25.0)	11 (64.7)	0.055	··	15 (45.5)	NA
	Non-AIDS defining events	4 (12.1)	2 (12.5)	2 (11.8)		··	4 (12.1)	
	Unknown	14 (42.4)	10 (62.5)	4 (23.5)		··	14 (42.4)	

*Wilcoxon rank sum test

Table 2: ART treatment and outcomes at 6 months according to receipt of early or late ART, based on cloning the data for all 190 eligible people, assigning one clone to each trial arm, and censoring at the time people deviated* from the regimen assigned to that clone.

		Early ART N=190	**Late ART N=190**
Outcome at 6 months	Artificially censored*	126	109
	Administratively censored (database close)	51	61
	Death	13	20
Started ART under this regimen?		56	68
Median (IQR) time (days) from CM diagnosis to starting ART		0 (0-7)	31 (23-42)
Type of ART received	PI based	39 (69.6)	35 (51.5)
	NNRTI based	14 (25.0)	29 (42.7)
	NRTIs only	1 (1.8)	1 (1.5)
	Other	2 (3.6)	3 (4.4)
Causes of death	AIDS defining events	9 (69.2)	9 (45.0)
	Non-AIDS defining events	2 (15.4)	1 (5.0)
	Unknown	2 (15.4)	10 (50.0)

* In the early ART arm, people were censored if they did not start ART within 2 weeks. In the late ART arm, people were censored if they started ART within 2 weeks or did not start ART within 8 weeks.

ACCEPTED MANUSCRIPT

DOI: 10.1093/cid/ciad122

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

Table 3: Comparison of present study with previously published RCTs of when to start ART in cryptococcal meningitis

		Present study (Europe/North America)		ACTG A5164 Trial (US/South Africa)		COAT Trial (Uganda/ South Africa)		Zimbabwe Trial	
Study period		1998-2009		2003-2006		2010-2012		2006-2009	
Antifungal therapy		IDSA**-based		IDSA**-based		Amphotericin B + Fluconazole		Fluconazole	
ART		Early	Deferred	Early	Deferred	Early	Deferred	Early	Deferred
N		56	68	13	23	88	89	28	26
Sex	Male	43	58	12	21	46	47	14	14
	Female	13	10	1	2	42	42	14	12
Age (years)	Median (IQR)	38 (34-45)	38 (33-43)	42 (34,43)	43 (29,48)	35 (28-40)	36 (30-40)	37 (8.5)	37.5 (6.9)
Race	White	15	23	5	1	0	0	0	0
	Black	14	17	2	11	88	89	28	26
	Other/unknown	27	28	6	11	0	0	0	0
Mode of HIV acquisition	Sex between men	15	27	NA	NA	0	0	0	0
	Sex between men and women	21	26			88	89	28	26
	Injecting drug use	9	7			0	0	0	0
	Other/unknown	11	8			0	0	0	0
Previous AIDS diagnosis		20	31	NA	NA	7	7	NA	NA
CD4+ T-cell count, cells/mm^3	Median (IQR)	20 (10-56)	23 (11-63)	32 (18,66)	25 (8,53)	19 (9-69)	28 (11-76)	27 (17–69)	51.5 (25–69)
VL, $\log_{10}$ copies/mL	Median (IQR)	5.4 (4.9-5.7)	5.2 (4.8-5.5)	5.2 (4.9-5.6)	4.9 (4.6,5.1)	5.5 (5.2-5.8)	5.5 (5.3-5.8)	4.97 (0.61)	5.21 (0.37)
Interval between CM diagnosis and ART initiation (days)	Median (IQR)	0 (0-7)	31 (23-42)	0 (0,0)	34 (29-39)	7 (6-7)	35 (34-35)	≤3 days	>70 days
Type of ART	PI-based	39	35	13	16	0	0	0	0
	NNRTI-based	14	29	0	3	88	89	28	26

ACCEPTED MANUSCRIPT

DOI: 10.1093/cid/ciad122

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

		Present study (Europe/North America)		ACTG A5164 Trial (US/South Africa)		COAT Trial (Uganda/ South Africa)		Zimbabwe Trial	
	NRTI-based	1	1	0	0	0	0	0	0
	Other/unknown	2	3	0	0	0	0	0	0
	Did not start	0	0	0	4	0	0	0	0
Mortality	Overall	5	7	0	4	41	29	23	12
	4 weeks	0	0	0	3	33	17	10*	7*
	6 months	5	7	0*	1	8	12		
Effect measure (Deferred versus early ART (ref))		Adjusted mortality hazard ratio, 1.39 (0.66,2.94).		Odds ratio for AIDS progression/deaths, 1.96 (95% CI: 1.06,3.70)		Mortality hazard ratio, 0.26 (95% CI: 0.09,0.71)		Adjusted mortality hazard ratio, 0.35 (95% CI: 0.14,0.91)	
Causes of death	CM	0	0	0	2	19	10	19	10
	Other AID defining event	2	0	0	1	4	6	1	1
	Non AIDS defining event	2	0	1	1	16	10	3	1
	Unknown	1	7	0	0	2	3	-	-

NA = Not available.

*<2 weeks

**Infectious Disease Society of America

ACCEPTED MANUSCRIPT

DOI: 10.1093/cid/ciad122

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023

FIGURE LEGENDS

Figure 1: Flow chart of exclusion and inclusion criteria of PWH

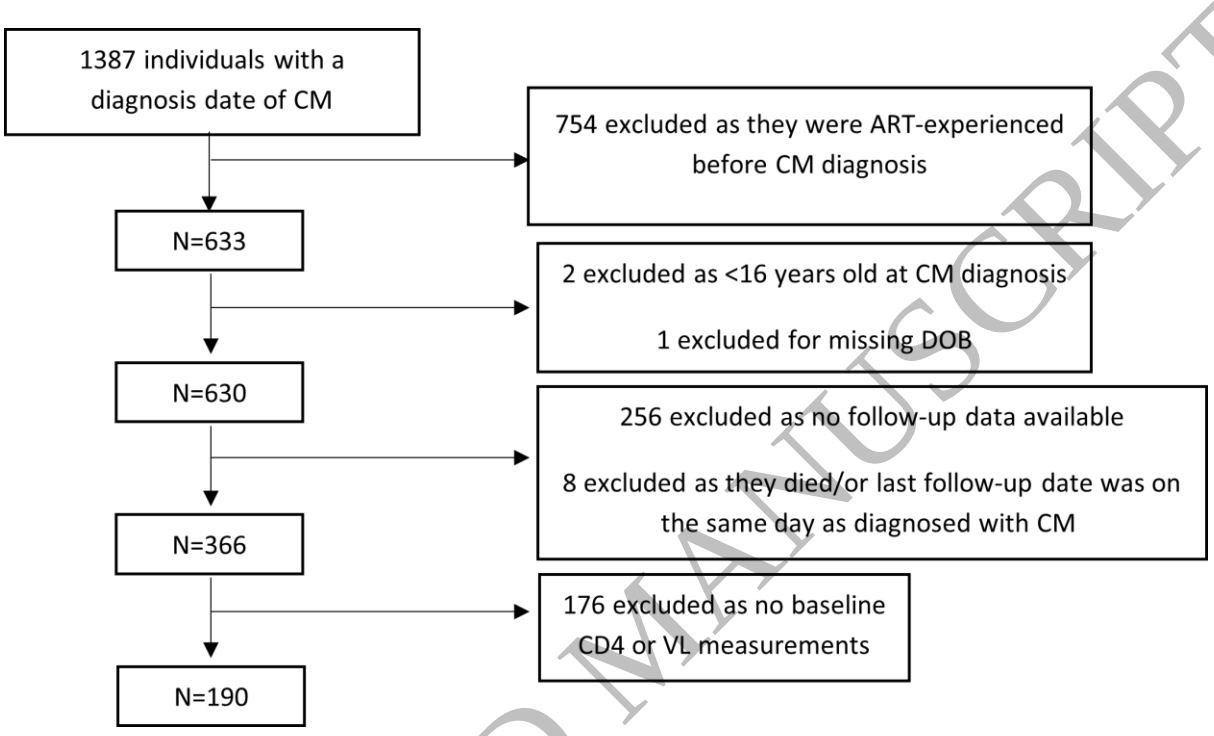
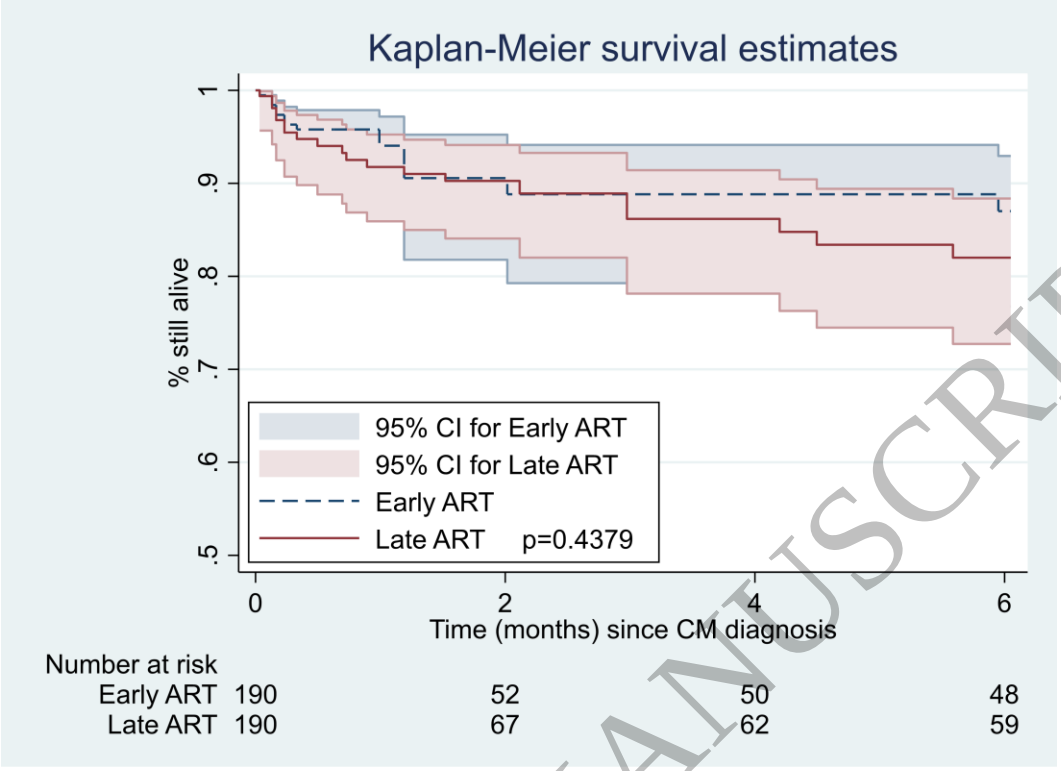


Figure 2: Estimated survival over time in PWH with cryptococcal meningitis according to whether they started ART early or late, using methods that mimic a randomized trial by cloning the data for each person and censoring at the time of deviation from the assigned regimen.

ACCECPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023



ACCEPTED MANUSCRIPT

Downloaded from https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciad122/7072297 by Universitaetsbibliothek Bern user on 09 March 2023